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EDITORIAL COMMENT

Diuretics

Are Our Ideas Based on Knowledge?*

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> *"The extent of our knowledge comes not only short of the reality of things, but even of the extent of our own ideas."*
>
> —John Locke,
> An Essay Concerning Human Understanding (1)

Although there is no doubt that diuretics are involved in the progression of heart failure, it is controversial whether they are detrimental or beneficial. Are they the culprit of mortality and morbidity or the means of preventing adverse consequences? Are these agents remnants of treatment from unenlightened times or the epitome of treatment that improves symptoms and outcomes? Fortunately, studies are now starting to address these important questions.

There is no question that diuretics improve symptoms. Despite the lack of good outcome studies, guidelines recognize the need for diuretics in order to improve symptoms and quality of life. Recently, however, they have been seen as necessary evils whose use should be minimized as much as possible.

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Suggestions that diuretics may be detrimental derive from the many studies that consistently demonstrate that patients receiving higher doses have worse outcomes (2). The hypothesis that diuretics (especially furosemide) cause deterioration is reasonable, as they cause neurohormonal activation, which, in turn, could exacerbate heart failure. Furthermore, diuretics can worsen renal function, and, with worsening renal function being prognostic, the connection between diuretics and outcomes seems logical. With publication of a study showing that furosemide increases cardiac dilatation in an animal model of heart failure, the conclusion that the use of diuretics should be minimized was obvious (3).

But the story is not that simple. Each step above has limitations that are only now being discussed. Yes, higher doses of diuretics are clearly associated with worse outcomes, but patients receiving higher doses are sicker and expected to have worse outcomes.

It also turns out that diuretics sometimes improve renal function. Renal perfusion might actually increase when central venous pressure decreases, a fact recognized more than a century ago (4). Recently, intra-abdominal pressure was shown to be associated with glomerular filtration rate, and the extent of reduction with diuresis was associated with improvement in renal function (5). It is possible that elevated right-sided pressures are associated with increased renal parenchymal pressure, which might decrease renal perfusion. Decreased renal perfusion secondary to increased renal afterload may also be the cause of impaired GFR in some fluid-overloaded patients. The importance of volume is supported by the association of right atrial pressure, but not cardiac index, with serum creatinine in the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial (6).

It is also not clear that declining renal function caused by diuresis engenders poorer outcomes. Clinicians often limit diuresis because of worsening renal function, but a recent study suggests that hemoconcentration is associated with improved outcome, even though it is also associated with increased serum creatinine (7). Similarly, DOSE (Diuretic Optimization Strategies Evaluation) (8) showed more diuresis and higher serum creatinine with higher diuretic doses, but no evidence that this had adverse consequences.

Even the neurohormonal activation associated with diuresis needs to be reconsidered in the age of neurohormonal blockade. Although the renin-angiotensin system is stimulated by volume contraction and stimulation of baroreceptors and the macula densa (9), the importance of these actions when angiotensin-converting enzyme inhibitors are used is unknown. Similarly, the adrenergic stimulation caused by heart failure is decreased by beta-adrenergic blockers. Furosemide may even have beneficial neurohormonal effects, decreasing sympathetic nervous system activity and stimulating renal production of prostaglandin E_2 (10).

And now Damman et al. (11) in this issue of the *Journal* provide provocative data suggesting that furosemide can *prevent* renal injury. Both urinary kidney injury molecule (KIM)-1 and urinary N-acetyl-beta-D-glucosaminidase (NAG) concentrations increased significantly after diuretic withdrawal and decreased with reinstitution of furosemide. High concentrations of these markers are potentially meaningful, as KIM-1 is up-regulated in proximal tubule cells after nephrotoxic or ischemic injury, NAG is released into the urine after renal proximal tubule injury, and both biomarkers are highly prognostic (12). Such findings suggest that fluid overload could be detrimental to the kidney or that furosemide is somehow protective.

Of course, however, this investigation does not answer the question regarding whether diuretics are beneficial or harmful to outcomes. The study is small, and the inconsistency of the findings is worrisome. If furosemide is protec-

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tive for the tubules, we would expect neutrophil gelatinase–associated lipocalin (NGAL) to be elevated in the serum and urine after furosemide's withdrawal; NGAL is upregulated after renal tubular injury (and may participate in limiting kidney damage) (13), and both urinary and serum NGAL are early markers of acute kidney injury, with prognostic importance (14). Surprisingly, serum and urinary NGAL were not significantly affected by the interventions of this study. The atrial natriuretic peptide data are also inconsistent, with atrial natriuretic peptide remaining elevated even after the reinstitution of furosemide.

The implications of the study by Damman et al. (11) are dependent on understanding the physiology of the renal biomarkers tested, but much remains to learn about these substances. There are differences in the time course and sensitivity of different biomarkers (15), and factors other than renal injury can impact their concentrations. With our present state of knowledge, we cannot make firm conclusions from the present study. Nevertheless, the study emphasizes that our ideas about diuretics are not equivalent to their reality. Only increasing knowledge will permit us to better use these commonly prescribed, and frequently disparaged, agents.

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